Pharmacy Update
March/April 1999

Drug Information Service
Pharmacy Department
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196

Charles E. Daniels, Ph.D.
Chief, Pharmacy Department

Editor
Karim Anton Calis, Pharm.D., M.P.H.
Coordinator, Drug Information Service, and Clinical Specialist, Endocrinology & Women's Health
kcalis@nih.gov

Associate Editor
Maryam R. Mohassel, Pharm.D.
Specialized Resident in Drug Information Practice and Pharmacotherapy
mmohassel@nih.gov

In This Issue

Paroxetine (Paxil®): A Brief Review

Paroxetine hydrochloride is a phenylpiperidine antidepressant structurally unrelated to other available antidepressants, including other selective serotonin reuptake inhibitors (SSRIs). It was approved for use in the United States in 1992. SSRIs have surpassed tricyclic antidepressants (TCAs) as first-line therapy for the treatment of major depression. Numerous clinical trials in patients with depression have shown the SSRIs to be equivalent to TCAs in efficacy, but superior in tolerability and safety.

Indications

Paroxetine is indicated for the treatment of depression, obsessive-compulsive disorder, and panic disorder.

Pharmacology

The mechanism of action of paroxetine is serotonin (5HT) reuptake blockade via inhibition of the serotonin reuptake transporter. Blockade of this transporter initially leads to increased concentrations of 5HT in the synaptic cleft. In response to increased 5HT, $5HT_{1A}$ autoreceptors act to decrease serotonin neurotransmission (auto-feedback mechanism). Chronic 5HT transporter blockade, unlike acute blockade, leads to downregulation (desensitization) of $5HT_{1A}$ and $5HT_{1B}/_{1D}$ autoreceptors which results in enhanced 5HT neurotransmission. 5HT autoreceptor downregulation is thought to confer the antidepressant effects of the SSRIs evident with chronic dosing. Paroxetine's inhibitory effects on the reuptake of norepinephrine and dopamine are minimal. Of the available SSRIs, paroxetine is the most potent inhibitor of 5HT reuptake. Paroxetine is more selective for serotonin (vs. norepinephrine) reuptake inhibition compared to fluvoxamine, sertraline, and fluoxetine. In contrast, citalopram has greater serotonin selectivity compared to paroxetine. The extent to which these differences in 5HT selectivity offer advantages in regards to efficacy remains to be determined. Paroxetine has negligible affinity for adrenergic, dopamine D_2, histamine H_1, and $5HT_2$ receptors and weak affinity for muscarinic cholinergic receptors.

Pharmacokinetics

Paroxetine is well absorbed from the gastrointestinal tract after oral administration. It undergoes extensive first-pass metabolism (partially saturable), estimated to be approximately 50 percent. Due to its highly lipophilic properties, paroxetine distributes widely in tissues including the central nervous system, with only one percent of the drug remaining in the systemic circulation. Paroxetine distributes into breast milk, with concentrations similar to those found in plasma. Advanced age and severe renal or hepatic impairment have been associated with increased paroxetine half-life and serum concentrations. Paroxetine is extensively metabolized in the liver by oxidation and methylation. Its glucuronide and sulfate metabolites are not pharmacologically active. Paroxetine is also partially metabolized by the cytochrome P450 (CYP) CYP2D6 isoenzyme. Saturation of this enzymatic pathway appears to account for the non-linearity of paroxetine's pharmacokinetics at high doses. Table 1 summarizes pharmacokinetic parameters (mean data only) of paroxetine compared to the other SSRIs.

Selected Clinical Studies

In general, paroxetine has shown superior efficacy compared to placebo and equal efficacy to TCAs and other SSRIs in the treatment of depression. Trials comparing paroxetine and TCAs have found similar efficacy (50 to 70 percent response) but better tolerability with paroxetine.

Table 1. Pharmacokinetic Parameters of Available SSRIs

Drug (active metabolite)	Bioavailability (Percent)	Plasma Protein Binding (Percent)	Volume of Distribution (L/kg)	Clearance (L/h)	Half-life (h)
Paroxetine	> 64	93	17	36	18
Fluoxetine	80	95	25	11	45
(Norfluoxetine)					168
Sertraline	> 44	98	25	96	26
(Desmethylsertraline)					71
Fluvoxamine	> 53	77	> 5	80	15
Citalopram	95	82	14	26	33

The rating scales widely used in depression clinical trials include the Hamilton Depression Rating Scale (HDRS) and the Montgomery Åsberg Depression Rating Scale (MADRS). Although rating scale endpoint scores can be compared to baseline scores to evaluate efficacy, a categorical response criterion of ≥ 50 percent decrease in rating scale score at endpoint is generally considered to reflect a clinically meaningful decrease in depressive symptoms. See Table 2 for a summary of treatment trials.

Table 2. Summary of Acute Treatment Trials*

	Population (Age, OP, IP)¶	Sample Size	Dose (mg/day)	Rating Scale	Responders (Percent)	Overall Efficacy
Placebo Trials						
Paroxetine vs. Placebo	40.6	163	10 - 50	HDRS	38	PAR>PC
	42.8	162			24§	
	34.5	32	10 - 50	HDRS	47	PAR>PC
	35.7	26			23	
	OP					
	44.9	33	10 - 50	HDRS	45	PAR=PC
	44.6	33		MADRS	24 (p<0.10)	
	34.9	34	10 – 50	HDRS	56	PAR>PC
	40.3	32		MADRS	25	
SSRI Trials						
Paroxetine vs. Fluoxetine vs. Placebo	41.3	55	20 – 50	HDRS	58	PAR=FLX= PC
	OP	54	20 - 80		57	
		19			53	
Paroxetine vs. Fluoxetine	44.6	37	20 – 40	HDRS,	68	PAR=FLX
	44.1	41	20 – 60	MADRS	63	
Paroxetine vs. Fluoxetine		60	20	HDRS	71	PAR = FLX
		61	20		67	
Paroxetine vs. Fluoxetine	43.0	89	20	MADRS	75	PAR = FLX
	44.7	87	20		78	
	IP					
Paroxetine vs. Fluvoxamine	43.7	56	20 – 30	HDRS	53	PAR = FLV
	43.4	64	50 – 200		50	
	IP & OP					
Paroxetine vs. Fluvoxamine	39.9	29	20 – 50	HDRS	NR	PAR = FLV
	42.7	29	50 – 150			
	OP					

¶OP = outpatient, IP = inpatients, § for this study clinical remission reported, more stringent criterion than response; PAR = paroxetine, FLX = fluoxetine, PC = placebo, FLV = fluvoxamine, NR = not reported

** All trials were at least 6 weeks in duration*

Adverse Effects

Common adverse effects associated with the use of paroxetine include headache, nervousness, tremors, insomnia, drowsiness, fatigue, nausea, and sexual dysfunction. Paroxetine has been associated with significantly more sedation compared to other SSRIs. To minimize daytime sedation, paroxetine is typically administered at bedtime.

One 12-week study evaluated paroxetine 20 mg/day, fluoxetine 20 mg/day, and placebo in depressed outpatients. Among all adverse events evaluated, the only side effect which differed significantly between the SSRIs was sexual dysfunction. Twenty-five percent of paroxetine-treated patients, versus seven percent of fluoxetine-treated patients, reported this side effect.

Sexual dysfunction, which includes loss of libido, inorgasmia, ejaculatory delay, and erectile dysfunction is a common side effect of SSRIs. Early clinical trials underestimated the incidence of sexual adverse effects because they relied on spontaneous reporting by trial participants. One descriptive study evaluating sexual dysfunction among 344 patients receiving SSRIs found little difference in the incidence of sexual dysfunction for patients receiving paroxetine, fluvoxamine, fluoxetine, or sertraline.

A discontinuation syndrome has also been described following cessation (usually abrupt) of SSRI therapy. The syndrome is characterized by dizziness or light-headedness, nausea, vomiting, headaches, lethargy, anxiety and/or agitation, tingling/numbness/"electric" shock-like sensations, tremors, sweating, insomnia, irritability, or diarrhea. These symptoms usually appear within 1 to 10 days of stopping the SSRI. For fluoxetine, the syndrome appears from 5 to 42 days after discontinuation of the drug. One open-label SSRI discontinuation trial reported higher rates of adverse events after abrupt discontinuation of paroxetine and sertraline compared to fluoxetine. However, the discontinuation period was of short duration (5 to 8 days), thereby favoring the fluoxetine treatment group.

Drug Interactions

Concomitant use of SSRI with monoamine oxidase inhibitors (MAOIs) may result in serotonin syndrome. SSRIs differ in their ability to inhibit various cytochrome P450 isoenzymes. Table 3 lists the relative potencies with which the SSRIs inhibit specific CYP isoenzymes. Selected examples of substrates for these isoenzymes include theophylline and caffeine (CYP1A2); phenytoin and warfarin (CYP2C); TCAs and

antipsychotics (CYP2D6); and cisapride, astemizole, and triazolobenzodiazepines (CYP3A4).

The mechanism for drug interactions involving SSRIs and warfarin is complicated. Alterations in the concentration of the inactive warfarin enantiomer can ultimately affect the active enantiomer. SSRIs most commonly associated with potential drug interactions with warfarin include fluoxetine, fluvoxamine, and paroxetine. One study evaluating a paroxetine-warfarin interaction found no significant increase in prothrombin time, but an increase in clinically significant bleeding was noted in 5 of 27 subjects when paroxetine 30 mg/day was added to warfarin 5 mg/day therapy. The exact mechanism of this interaction is unknown.

Table 3. CYP Inhibition Potential of SSRIs

	Paroxetine	Fluoxetine	Sertraline	Fluvoxamine	Citalopram
CYP1A2	+	+ (+)	+ (+)	+++	+
CYP2C9	+	++ (++)	+ (+)	++	0
CYP2C19	+	++ (++)	++ (++)	+++	0
CYP2D6	+++	+++ (+++)	+ (+)	+	0 (+)
CYP3A4	+	+ (++)	+ (++)	++	0

Effect of metabolite is shown in parentheses.

0 = minimal or zero inhibition, + = mild, ++ = moderate, +++ = strong

Precautions

Due to the wide safety index of the SSRIs, few serious adverse events have been reported with increased doses or plasma concentrations. Paroxetine's elimination half-life appears to be prolonged in the geriatric population. For patients exhibiting renal (creatinine clearance <30 mL/min) and/or hepatic dysfunction, paroxetine should be initiated at the lower dose of 10 mg/day and titrated to a maximum of 40 mg/day.

Contraindications

Concomitant use of paroxetine in patients taking MAOIs or other SSRIs is contraindicated. These combinations can result in a serious, sometimes fatal, serotonin syndrome. This syndrome is characterized by hyperthermia, rigidity, myoclonus, and autonomic instability with possible fluctuations of vital signs and mental status changes. Paroxetine should not be used within 14 days of discontinuing an MAOI. Similarly, it is recommended that MAOI therapy not be initiated until 14 days have elapsed following paroxetine discontinuation.

Dosage and Administration

Paroxetine is administered as a single daily dose, initiated at 20 mg/day. Although the package insert specifies drug administration in the morning, patients experiencing sedation may opt for nighttime administration. For patients not showing an adequate therapeutic response within 2 to 3 weeks of paroxetine initiation, the dose may be increased in 10 mg increments at weekly intervals. The usual dose range in the treatment of depression is 20 to 50 mg/day. For elderly patients and those with renal and/or hepatic dysfunction, doses are initiated at 10 mg/day and titrated to a maximum of 40 mg/day.

Table 4. Cost*

SSRI	Dose	Cost Per Month
Paroxetine 20 mg tablet	20 mg/day	$31.02
Fluoxetine 20 mg capsule	20 mg/day	$38.82
Sertraline 50 mg tablet	50 mg/day	$37.68
Citalopram 20 mg tablet	20 mg/day	$33.13
Fluvoxamine 100 mg tablet	100 mg/day	$39.17

Paroxetine and fluoxetine are also available as liquid formulations.

** Federal Supply Schedule*

Conclusion

Paroxetine is a selective and specific serotonin reuptake inhibitor with demonstrated efficacy and tolerability in the acute treatment of depressed patients. It is as effective as TCAs and other SSRIs in the acute treatment of depression. Paroxetine exhibits a favorable pharmacokinetic profile, including a relatively short half-life (compared to fluoxetine) and lack of active metabolites. The adverse event profile of paroxetine is similar to that of other antidepressants in this class, but paroxetine may be associated with more sedation. As with other SSRIs, a discontinuation syndrome is possible with abrupt cessation. When discontinuing paroxetine, tapering of the dose is suggested. Paroxetine potently inhibits CYP2D6, but it shows little clinically relevant inhibition of other cytochrome P450 isoenzymes.

References available upon request.

Did You Know ...

- An estradiol transdermal patch (Climara®) was recently approved for the prevention of postmenopausal osteoporosis. This is the only once-a-week transdermal estrogen product approved for osteoporosis prevention.
- The FDA recently approved alitretinoin 0.1% (Panretin®) for the topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma. This is the first topical agent approved for this condition.
- Cilastazol (Pletal®) has been approved for reduction of symptoms associated with intermittent claudication. The dose of cilastazol may need to be decreased in patients receiving concomitant treatment with agents known to inhibit the cytochrome P450 3A4 isozyme (e.g., azole antifungals or certain macrolide antibiotics).
- Telmisartan (Micardis®), a new angiotensin II receptor inhibitor, was recently approved for the treatment of hypertension.
- Lovastatin (Mevacor®) was approved for the primary prevention of coronary heart disease in patients diagnosed with hypercholesterolemia.

Formulary Update:

The Pharmacy and Therapeutic Committee recently approved the following formulary actions:

Additions:

- Thyrotropin alfa (Thyrogen®), a highly purified recombinant form of human thyroid stimulating hormone (TSH) for use as an adjunctive diagnostic tool for serum thyroglobulin testing with or without radioiodine imaging.
- Paroxetine (Paxil®), a selective serotonin-reuptake inhibitor indicated for the treatment of depression, obsessive-compulsive disorder, and panic disorder.
- Octreotide acetate (Sandostatin LAR® Depot), a long-acting octreotide formulation administered once monthly by intramuscular injection. It is indicated for the treatment of acromegaly, and diarrhea and flushing associated with metastatic carcinoid tumors or vasoactive intestinal peptide tumors.
- Ropivacaine (Naropin®), a long-acting amide local anesthetic indicated for local or regional anesthesia for surgery, postoperative-pain management, and obstetrical procedures.
- Abacavir (Ziagen®), a nucleoside reverse transcriptase inhibitor of HIV-1 for use in combination with other antiretroviral agents in the treatment of HIV infection.
- Trastuzumab (Herceptin®), a recombinant humanized monoclonal antibody (rhuMab) indicated for the treatment of metastatic breast cancer in patients who present with an overexpression of the human epidermal growth factor receptor-2, c-erbB2.
- Botulinum toxin type A (Botox®), a lyophilized form of purified botulinum toxin indicated for the treatment of strabismus and blepharospasm.
- Abciximab (ReoPro®), a Fab fragment of the chimeric human murine monoclonal antibody 7E3 used as an adjunct to percutaneous transluminal coronary angioplasty for the prevention of acute cardiovascular ischemic complications.
- Rituximab (Rituxan®), a chimeric monoclonal antibody indicated for the treatment of patients with relapsed or refractory low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma.

Deletions:

- Domeboro® Otic Solution
- Humorsol® Ophthalmic Solution
- Cortisporin® Ophthalmic Solution
- Cortisporin® Ophthalmic Ointment

Editors' Note

We wish to thank Cara L. Alfaro, Pharm.D., BCPP for her contribution to this issue of *Pharmacy Update*.

Drug Information Service
Pharmacy Department
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196